REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following reasons.

I. Status of the Claims

Claims 4-5, 9-15, 17, 53-54, 58-63 and 73 were previously cancelled. Claims 74-86 and 89 are cancelled in this response without prejudice or disclaimer thereof. Applicants reserve the right to pursue the subject matter of any cancelled claim in one or more continuing applications.

Claims 7, 8, 56, 57, 92 and 93 have been amended to add the term "about." The term "about" was deleted from the original claims 7, 8, 56 and 57 in the prior response. Claim 26 has been amended to be consistent with claim 1. Claims 32, 43, 48 and 49 have been amended to delete the term "about" following the phrase "less than" or "greater than." Claim 56 has been amended to correct a typographical error. Claims 16, 64 and 97 have been amended to correct antecedent basis. Claim 88 has been amended to correct dependency. Claim 95 has been amended to delete the term "cationic."

Applicants acknowledge the finality of the outstanding Office Action. The claim amendments: (i) do not introduce any new matter; (ii) are made to correct a typographical error or improper claim dependency, to cancel claims, to delete terms, or to add back terms which appeared in the original claims but was deleted in the prior amendment; (iii) are made in keeping with the Examiner's suggestions; (iv) do not require any additional search; and (v) place the application in condition for allowance or at least in better condition for appeal. Therefore, Applicants respectfully request entry of this amendment. Upon entry, claims 1-3, 6-8, 16, 18-52, 55-57, 64-72, 87-100 will be pending, with claims 26-49 withdrawn from consideration. Applicants respectfully request rejoinder of the withdrawn method claims for examination upon allowance of the corresponding composition claims.

II. Statement of the Substance of the Interview

Applicants thank Examiner Susan Tran for the courtesies extended during an interview with Applicants' representative, Yang Tang, on July 29, 2010. During the interview, the species election requirement set forth in the final Office Action dated May 26, 2010 was discussed. Applicants were required to elect a species of an anionic surface stabilizer, a cationic surface stabilizer, an ionic surface stabilizer, or other. *See* final Office Action, page 2, 2nd paragraph. Examiner Tran confirmed that removing the species of surface stabilizers recited in the claims would moot the requirement. Accordingly, solely for the purpose of advancing prosecution and without prejudice to Applicants' right to claim this subject matter, claims 74-86 and 89 are now cancelled.

The rejection under 35 U.S.C. §112, first paragraph, was also discussed during the interview. More specifically, Examiner Tran confirmed that amendments to claims deleting the term "about" following the phrase "less than" or "greater than" or adding the term "about" following the term "from" or "to" would overcome the rejection. Accordingly, Applicants have amended claims at issue in keeping with the Examiner's suggestion.

Because the claim amendments are to be made to cancel claims, to delete terms, or to add back terms which appeared in the original claims but deleted during prosecution, Examiner Tran agreed to enter the claim amendments submitted in response to the final Office Action.

III. Response to Species Election Requirement

The Examiner imposed a species election requirement for Applicants to elect a species from an anionic surface stabilizer, a cationic surface stabilizer, an ionic surface stabilizer or other surface stabilizer. *See* final Office Action, page 2. The claims at issue have been cancelled thereby rendering the requirement moot.

IV. Claim Objections

Claim 56 is objected to for reciting a percentage inconsistent with that of other pending claims. Claim 56 has been amended to correct the typographical error thereby obviating the basis for the objection.

V. Rejection of Claims under 35 U.S.C. §112, first paragraph

Claims 1-3, 6-8, 16, 18-25, 50-52, 55-57, 64-72 and 74-100 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack written description. Applicants respectfully traverse the rejection.

The Examiner rejects the claims reciting the term "about" following the phrase "less than" or "greater than" and the claims missing the term "about" following the term "from" or "to." As discussed in section II above, the claims at issue have been amended upon a telephonic consultation with the Examiner.

Claims 80 and 82 have been cancelled.

Claim 95 has been amended to delete the term "cationic," which lacks antecedent basis in the base claim.

The Examiner asserts that the term "C_{max}" recited in claims 16, 64, 83 and 97 lacks antecedent basis. Claims 16, 64 and 97 are amended for clarity. Claim 83 is cancelled.

VI. Rejection of Claims under 35 U.S.C. §103(a)

A. Struengmann & Liversidge

Claims 1-17, 50-67, 74-83 and 87-97 are rejected under 35 U.S.C. §103(a) for allegedly being obvious over PCT Publication No. WO 99/09988 by Struengmann et al. ("Struengmann")

in view of PCT Publication No. WO 93/25190 by Liversidge et al. ("Liversidge"). Applicants respectfully traverse the rejection.

(i) Struengmann fails to meet several claim limitations in addition to the lack of a teaching of the claimed particle size.

The Examiner acknowledges that Struengmann's composition comprises "micronized meloxciam" and cites Liversidge to compensate for Struengmann's deficiency in the teaching of the claimed particle size. In fact, Struengmann also fails to teach, for example, a surface stabilizer "adsorbed on the surface of the meloxicam particles," a surface stabilizer "essentially free of intermolecular cross-linkages," as recited in claims 1, 50 and 87, and the specific surface stabilizers polyvinylpyrrolidone and sodium deoxycholate, as recited in claims 1 and 50.

Applicants note these additional deficiencies in Struengmann not to argue the reference individually, but because the basis for the Examiner's rejection is that Struengmann is the primary reference teaching each and every limitation of the claimed invention but for the particle size. Struengmann fails to fairly teach or suggest numerous other claim limitations, including the specific particle size. Struengmann fails to teach the specific surface stabilizers, their structural relationship to the particles, and that they are free of intermolecular cross-linkages. Thus, to combine the references as proposed in the rejection (to simply render the particles of Struengmann in the size of Liversidge) is not a straight-forward exercise as set forth by the rejection. For even if a person of ordinary skill in the art were to do this, (reduce the particles of meloxicam in Struengmann to the claimed range), Struengmann still fails to teach the specific surface stabilizers, their structural relationship to the particles, and that they are free of intermolecular cross-linkages.

Although use of surface stabilizers is described by Liversidge, one skilled in the art would not have any reason to use a surface stabilizer for Streungmann's composition. As the Examiner agrees, Streungmann's composition comprises micronized meloxicam, which does not requires

the presence of a surface stabilizer adsorbed on the surface of meloxicam particles to prevent agglomeration or aggregation.

(ii) The articulated reason to combine the cited references has been accomplished by Struengmann.

The Examiner contends that "one of ordinary skill in the art would have been motivated to, by routine experiment[,] optimize the particle size..." because Liversidge teaches reducing particle size to obtain a higher bioavailability.

Liversidge may fairly teach or suggest reduction in particle size to obtain higher bioavailability, but there is no reason for one skilled in the art to do this to the meloxicam of Struengmann because Struengmann already employs techniques to improve solubility and bioavailability. Struengmann discloses a solution for improving solubility and bioavailability "by mixing meloxicam with special additives" rather than by reducing the particle size to the nanoparticulate range. The special additives include surfactants, co-solvents, hydrotropic agents, alkalizing agents, cyclodextrins, hydrocolloids and polymers. *See* page 3, lines 4-16. There is no suggestion by Struengmann that its methods for improving dissolution and bioavailability are in anyway insufficient and 1) would benefit by further reduction in particles size in view of Liversidge, and/or 2) would be possible using the techniques described in Liversidge.

First, there is nothing in Struengmann to suggest that further reduction in the size of meloxicam will achieve greater bioavailability compared to the increased bioavailability already achieved with mixing special additives with meloxicam. Such a conclusion may be drawn from at least Examples 1 and 2, Tables 1 and 2, of Struengmann (Pages 7-9). In these examples, Struengmann dry ball mills meloxicam and various co-solvents. In order to determine the enhanced dissolution effect of the co-solvents, Struengmann uses as a control, a formulation that was dry ball milled, but without co-solvents. Table 2 clearly shows that the addition of co-solvents increase dissolution compared to a formulation of similar particle size. A person of ordinary skill in the art reading Struengmann for all it teaches would, if desiring to increase

dissolution of meloxicam, would not be led to reduce the particle size, but to add a co-colvent because co-solvents have a greater impact on dissolution than particle size reduction.

Second, it is unclear how or at what stage of making the formulation of Struengmann would one of ordinary skill in the art employ the particle reduction techniques of Liversidge. Liversidge, at pages 8 and 9, describes adding the surface stabilizer and drug into a liquid medium in which the drug is not soluble. This composition is then milled, and the resulting liquid dispersion is harvested. Struengmann describes co-grinding the drug with various co-solvents. Some co-solvents are liquid at room temperature and some are dry powders. If meloxicam is placed into water (a liquid medium in which the drug is not soluble) then the co-solvents of Struegnman would act to dissolve meloxicam during the milling process of Liversidge. If one removed the co-solvents of Struengmann, one is modifying the reference contrary to its intended purpose.

Accordingly, the articulated reason to combine or modify the primary reference, i.e., Struengmann, has already been satisfied by its own teachings using a different approach of employing additives and one skilled in the art could not employ the techniques in Liversidge to the meloxicam of Struengmann without destroying the intended purpose of Struengmann.

(iii) The teachings of Liversidge in combination with Struengmann would not have rendered the claimed invention obvious, either.

The Examiner points out that "Liversidge teaches a process suitable for a wide variety of NSAIDs including oxicam" (final Office Action, page 7, lines 11-12). In order to advance prosecution, Applicants preemptively rebut a rejection in which Liversidge is used as the primary reference where one might state that it would be obvious to select the meloxicam of Struengmann in the process of Liversidge. Liversidge fails to expressly state meloxicam as an exemplary NSAID. Liversidge does disclose many exemplary NSAIDs at page 4, line 16, through page 5, line 4, and oxicam is one of the exemplified subgenus. Pursuant to MPEP

2144.08, the prior-art teaching of a genus does not necessarily renders the claimed species obvious. *See* the discussion submitted in the response filed on June 29, 2009, pages 31-32.

Moreover, Liversidge discloses numerous surface modifiers at page 5, line 10, through page 6, line 24. In the absence of any teaching or fair suggestion from the cited reference, one skilled in the art would not have considered it obvious to select polyvinylpyrrolidone and sodium deoxycholate as the surface stabilizers, to obtain the claimed invention prescribed by claims 1 and 50.

(iv) The claimed invention achieves unexpected results.

As demonstrated in Example 3 of the specification, nanoparticulate meloxicam compositions, in both liquid dosage form and in solid dosage form, achieved ***significantly improved*** pharmacokinetic profiles *in vivo* in comparison to a conventional, microparticulate meloxicam composition, MOBIC®. More specifically, the improved C_{max}, T_{max} and AUC are summarized in Table 1 below.

Table 1

Formulation	C_{max} (relative % in comparison with MOBIC®)	T_{max} (relative % in comparison with MOBIC®)	AUC (relative % in comparison with MOBIC®)
Liquid dispersion comprising nanoparticulate meloxicam and Poloxamer 407	126%	22%	118%
Lyophilized wafer comprising nanoparticulate meloxicam, polyvinylpyrrolidone and docusate sodium	124%	38%	107%

Moreover, the claimed meloxicam compositions achieved superior stability. A number of nanoparticulate meloxicam formulations were tested for stability under different storage temperature, 5°C, 25°C, or 40°C, for a period of two months. The nanoparticulate meloxicam

compositions exhibit superior stability even at lower or elevated temperature for an extended period of time, as detailed in Table 2 below.

Table 2

Formulation	Storage time Days	Condition °C	Dmean nm	D50 nm	D90 nm
2.5% meloxicam, 0.5% Pvp K17	30	25	157	95	334
	30	40	295	259	476
2.5% meloxicam, 0.5% Pvp K17, 0.25% NaDOC	60	5	99	89	121
	60	25	101	90	127
	60	40	106	91	145
2.5% meloxicam, 0.25% Pvp K17, 0.25% Tween 80	29	5	273	256	417
	29	25	468	446	710
	29	40	585	566	858
2.5% meloxicam, 0.5% Pvp K12, 0.25% NaDOC	62	5	102	89	130
	62	25	104	91	137
	62	40	106	91	148
2.5% meloxicam, 0.5% Tween 20, 0.5% Span 20	29	5	113	89	225
	29	25	451	425	696
	29	40	548	537	825
2.3% meloxicam, 0.5% Pvp K17, 2.3% PEG400, 0.23% NaDOC	0	NA	123	105	214
2.5% meloxicam, 0.5% Pvp K17, 0.25% NaDOC, 200mM Sodium Phosphate pH 9	7	5	139		
2.5% meloxicam, 0.5% Pvp K17, 0.125% NaDOC, 125mM Sodium Phosphate pH 7.5	14	5	139		
2.3% meloxicam, 0.46% Pvp K17, 0.23% NaDOC, 50mM Sodium Phosphate pH 6	7	5	102		
2.7% meloxicam, 0.54% Pvp K17, 200mM Sodium Phosphate pH 9	14	5	164		
2.5% meloxicam, 0.5% Pvp K17, 0.08% NaDOC, 0.1M Potassium Phosphate pH 7.5	0	5	115		
3.4% meloxicam, 0.68% Pvp K17, 0.23% NaDOC, 0.68% Tween 80, 100mM Sodium Phosphate pH 8	0	5	220		

Furthermore, an exemplary injectable nanoparticulate meloxicam formulation comprising polyvinylpyrrolidone and sodium deoxycholate was tested in human patients in comparison to the commercially available, microparticulate meloxicam tablet, MOBIC®. The nanoparticulate meloxicam formulation consistently achieved significantly increased blood plasma drug concentration in all patient groups as represented by AUC_{last} and AUC_{inf} in Table 3 below.

Table 3				
Meloxicam Dosage (mg)	AUC (ng*hr/mL)	Nanoparticulate meloxicam injectable formulation	MOBIC® tablet	% of increase of AUC by nanoparticulate formulation
Cohort (15 mg)	Last	46094.8 (14565.8)	42949.2 (11662.8)	107%
	Inf.	57314.4 (27233.2)	53988.8 (23207.7)	106%
Cohort 2 (30 mg)	Last	92575.9 (18456.0)	88340.6 (16547.1)	105%
	Inf.	107508.7 (34443.0)	104400.0 (30656.2)	103%
Cohort 3 (60 mg)	Last	156042.6 (24041.4)	146677.3 (21925.3)	106%
	Inf.	171229.0 (34439.1)	163854.7 (32916.7)	105%

In view of the significant and unexpected results achieved by the claimed invention, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a).

B. Struengmann, Liversidge, Desai & Courteille

Claims 1-17, 50-67, 74-83 and 87-97 are rejected under 35 U.S.C. §103(a) for allegedly being obvious over Struengmann in view of Liversidge and PCT Publication No. WO 01/45706 by Desai et al. ("Desai") or U.S. Patent No. 5,384,124 to Courteille et al. ("Courteille"). Applicants respectfully traverse the rejection.

The teachings of Struengmann and Liversidge are discussed *supra*. Desai or Courteille is cited for the alleged teaching of a second particle population having a different particle size range. However, the teachings of Desai and Courteille do not address the deficiencies as stated in section A above. Accordingly, the claims at issue are non-obvious for depending from non-obvious base claims.

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the

undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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